REMARKS

Claims 1, 4-7, 11, 21-27, 30-35, and 37-44 are pending in the application. Claims 2, 3, 8-10, 12-20, 28, 29, and 36 have been canceled without prejudice, and claims 30-33 have been amended. Support for the amendments can be found in the specification at, e.g., page 26, lines 10-21; and page 63, line 16, to page 64, line 3. These amendments add no new matter.

35 U.S.C. §112, First Paragraph (Enablement)

At pages 2-4 of the Office Action, the Examiner rejected claims 5, 22-27, 30-33, and 35-44 as allegedly not enabled.

With respect to the rejection of claims 5 and 22-27, the Examiner stated that

> [c]laims 5, 22 and 25 have been amended to incorporate the limitation "polypeptide stimulates apoptosis"... The specification does not teach a cell type that would be expected to provide the appropriate upstream molecule or molecules which would interact with the LRR domain of PYRIN-5, therefore the transduction of any given cell with a nucleic acid encoding a protein which is 85%, 95% or 98% identical to SEQ ID NO:6 would not guarantee that said protein would encounter the necessary molecule or molecule which would bind the LRR domain of the variant, alter the conformation of the pyrin domain in such a way as to enable interaction with the downstream signaling molecules(s) in order to effect apoptosis necessary to fulfill the requirements of claims 5, 22-27.

Applicants respectfully traverse the rejection of claims 5 and 22-27 in view of the following comments.

As detailed in the specification, the PYRIN-5 polypeptide (SEQ ID NO:6) contains a pyrin domain, a nucleotide binding site, and several leucine rich repeats (page 3, lines 16-29). PYRIN-5 belongs to the NACHT NTPase family of proteins, members of which have been implicated in the regulation of apoptosis (page 5, lines 1-9). The specification states that, as a result of the expected role of PYRIN-5 in the regulation of cell death, modulators of PYRIN-5 expression or activity can be used to treat disorders associated with inappropriate apoptosis, including neurological disorders associated with neuronal apoptosis (page 28, line 29, to page 29, line 3).

The disclosure contained in the specification as filed regarding the role of PYRIN-5 in cell death signaling has been further confirmed by experiments carried out by and under the direction of Frederick Lo of Wyeth. These experiments, which are described in the accompanying Declaration of Mr. Lo Under 37 C.F.R §1.132, demonstrate that PYRIN-5 expression is elevated in injured neurons (see Paragraph 3 of Declaration), that PYRIN-5 is expressed in transient focal ischemia (see Paragraph 4 of Declaration), and that PYRIN-5 induces neuronal apoptosis (see Paragraph 5 of Declaration). These studies of Mr. Lo clearly demonstrate that, as described in the specification, PYRIN-5 functions in the regulation of apoptosis.

Because PYRIN-5 is expressed in injured neurons and stimulates apoptosis, the nucleic acids of claims 5 and 22-27 encode polypeptides that can be used for identifying candidate compounds for modulating cell death signaling (see specification at, e.g., page 4, lines 5-14). For example, encoded PYRIN-5 polypeptides can be used to screen for compounds that modulate the ability of PYRIN-5 to stimulate apoptosis. Such compounds are expected to be potentially useful therapeutic compounds for the regulation of cell growth and death.

The passage above reproduced from the Office Action asserts that the specification does not teach a cell type that would be expected to have the appropriate upstream or downstream molecules to enable PYRIN-5 to stimulate apoptosis. However, and contrary to this assertion, the specification discloses that apoptosis is a mechanism of cell death in a wide variety of neurological diseases characterized by the gradual loss of specific sets of neurons (page 7, line 35, to page 8, line 26). Furthermore, with respect to the role of PYRIN-5 in stimulating apoptosis in neuronal cells, the specification discloses that neurological disorders associated with neuronal apoptosis can be treated by modulating the expression or activity of PYRIN-5 (page 28, lines 29-33). As a result, the skilled person would readily understand that neuronal cells contain the molecules necessary to enable PYRIN-5 to stimulate apoptosis.

The enclosed declaration of Mr. Lo confirms that transfection of a variety of cell types (including but not limited to neuronal cells) with a cDNA encoding PYRIN-5 results in the stimulation of apoptosis. Accordingly, and consistent with the teachings of the specification, it

would have required no undue experimentation for the person of ordinary skill in the art to express a PYRIN-5 nucleic acid in a cell (e.g., a neuronal cell) such that the transfection results in stimulation of apoptosis.

With respect to the rejection of claims 30-33, the Examiner stated that

> [c]laims 30-33 are drawn to an isolated nucleic acid molecule that encodes a polypeptide comprising residues 1-91, 188-506 or 688-1056 of SEQ ID NO:6. The specification teaches that residues 1-91 of SEQ ID NO:6 are the pyrin domain, residues 188-506 are the NBS domain and residues 688-1056 are the LRR domain. The specification provides no teachings as to the structural variations which could be tolerated by PYRIN-5 wherein said structural variations would result in a variant molecule having the ability to expose the pyrin domain within the molecule upon binding of an upstream molecule to the LRR domain... It is noted that the specification does not teach a use for such a protein which would not mediate apoptosis in the same manner as SEQ ID NO:6. Due to these reasons, one of skill in the art would be forced into undue experimentation in order to make and use the broadly claimed nucleic acids which minimally encode the isolated domains of SEQ ID NO:6.

Applicants respectfully traverse the rejection of claims 30-33 in view of the claim amendments and the following comments.

As detailed herein, the present application describes the identification of a protein designated PYRIN-5. PYRIN-5 has an N-terminal pyrin domain (at about amino acid residues 1-91 of SEQ ID NO:6), a nucleotide binding site (NBS; at about amino acid residues 188-506 of SEQ ID NO:6), and several C-terminal leucine rich repeats (LRR) which form an LRR domain (at about amino acid residues 688-1056 of SEQ ID NO:6) (see specification at page 31, line 26, to page 32, line 3).

Amended independent claim 30 is directed to an isolated nucleic acid comprising a nucleotide sequence that encodes a fusion protein consisting of amino acid residues 1-91, 188-506, or 688-1056 of SEQ ID NO:6 and a heterologous polypeptide. Exemplary "heterologous polypeptides" include sequences (such as GST) that can be used to facilitate purification of a recombinant fusion protein (see, e.g., specification at page 64, lines 4-19). Because the fusion protein encoded by the claimed nucleic acid contains an intact PYRIN-5 functional domain (i.e.,

a pyrin, NBS, or LRR domain), the encoded fusion protein necessarily retains the functional activity of the respective domain.

A "pyrin" domain, so-named for its homology to a portion of pyrin (marenostrin), is an effector domain thought to be involved in homophilic protein-protein interactions (see, e.g., specification at page 4, lines 5-14). As a result of the functional importance of the pyrin domain, the pyrin domain-containing fusion protein encoded by the nucleic acid of claim 30 or claim 31 can be used to screen for agents (e.g., peptides, peptidomimetics, small molecules or other drugs) that bind to the pyrin domain of PYRIN-5 and/or modulate the activity of the pyrin domain of PYRIN-5 (see, e.g., specification at page 95, line 31, to page 96, line 5). Agents identified by such screening assays are expected to be potentially useful therapeutic compounds for the regulation of cell growth and death.

An NBS is present in a number of proteins that transmit signals that activate apoptotic and inflammatory pathways in response to stress and other stimuli (see, e.g., specification at page 5, lines 1-9). The NBS (about amino acids 188-506 of SEQ ID NO:6) of PYRIN-5 is expected to bind to and hydrolyze a nucleotide triphosphate (ATP or GTP). A fusion protein containing the NBS of PYRIN-5 is expected to necessarily bind to a nucleotide. As a result, the fusion protein of claim 30 or claim 32 can be used to screen for compounds that modulate the nucleotide-binding ability of the NBS of PYRIN-5 (see, e.g., specification at page 28, lines 22-28). Nucleotide binding assays and methods of detecting the hydrolysis of a nucleotide triphosphate by a protein containing an NBS are well known to those of skill in the biological arts and described in detail in the specification at, e.g., page 96, line 15, to page 97, line 11. Compounds identified by such screens can be used to modulate PYRIN-5-mediated signal transduction and therefore modulate, for example, PYRIN-5-mediated apoptosis.

An LRR domain is a functional domain present in a number of proteins involved in apoptotic and inflammatory pathways. The LRR domain of PYRIN-5 is expected to interact with molecules associated with stress, infection, and/or inflammation (see, e.g., specification at page 5, lines 10-14). Similar to the screens described herein for fusion proteins containing a pyrin domain or an NBS, screening assays can be performed to identify molecules that bind to

the LRR domain of PYRIN-5 and/or modulate the activity of the LRR domain of PYRIN-5 (see, e.g., specification at page 95, line 31, to page 96, line 5; and page 97, lines 12-15). Compounds identified by such screens are expected to, as a result of their ability to bind to and/or modulate the activity of the LRR domain of PYRIN-5, constitute potentially useful therapeutic compounds for the regulation of apoptosis.

In light of the foregoing comments and claim amendments, applicants respectfully submit that the teachings of the specification combined with the level of skill in the art at the time of filing of the present application enabled the person or ordinary skill in the art to make and used the claimed nucleic acids without undue experimentation and with a reasonable expectation of success. Accordingly, applicants request that the Examiner withdraw the rejection of claims 5, 22-27, 30-33, and 35-44.

CONCLUSION

Applicants ask that all claims be allowed in view of the amendments to the claims and the remarks contained herein.

Enclosed is a Petition for One Month Extension of Time and a check for the Petition fee. Please apply any charges or credits to deposit account 06-1050, referencing Attorney Docket No. 16953-002001.

Respectfully submitted,

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